Neutral Ionophores having Extraordinary Ca^{2+} Binding Strengths and Ca^{2+}/Na^{+} Selectivities in Aqueous Solution

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The highest divalent calcium cation binding constants and Ca^{2+}/Na^{+} selectivities ever observed in aqueous solution for neutral crown ether derivatives are reported: for 4,13-diaza-18-crown-6 derivatives having -gly-gly-OCH_2CH_3 or -gly-ala-OCH_2CH_3 sidearms, K_S values in water are, respectively, $10^{6.6}$ and $10^{7.8}$ and the Ca^{2+}/Na^{+} selectivities in water for these two compounds are, respectively, $>10^4$ and $>10^5$.

Despite its obvious biological relevance, very little is known about Ca^{2+} binding by neutral ionophores.[1] Ion-selective electrode methods[2] (Na^+ and K^+), and NMR methods (Na^+) are much less attractive for either K^+ or Ca^2 although the latter can now be assessed by ISE methods.[3] We now report that dipeptide derivatives of 4,13-diaza-18-crown-6 (**1**) and certain three-armed derivatives of 4,10-16-triaza-18-crown-6 (**2**) exhibit extraordinarily high Ca^{2+}-binding strengths and remarkable Ca^{2+}/Na^{+} cation binding selectivities.

The bibracchial[4,5] and tribracchial[6] lariat ether derivatives were prepared by the previously reported methods.[5,6] The cation binding strengths[2] and thermodynamic parameters,[7]† were determined by previously published methods except that Ca^{2+}-binding strengths in water were determined directly by using a divalent calcium electrode.[7] The stability constants and selectivities are summarized in Table 1.

The entries for the simple crown ether and the cryptand compounds are literature values that are included as benchmarks. The $3n$-crown-n compounds do not obey a simple 'hole-size' relationship[3] as is the case for the cryptands. Both classes of compounds show solvent dependent cation binding constants, however.[1] The decrease for the $3n$-crown-n series (n = 4–6) is about 10^2 between methanol and water and for the cryptands the decrease is even greater. The lariat ethers show the same trend for Na^+. It is remarkable, therefore, that certain of the two-armed lariat ethers show the opposite trend, at least as so far determined, for the Ca^{2+} cation. The log K_S value for Na^+ bound by 18-crown-6 in MeOH is 4.35 and is between 0.5—1.8 in water.[1,8e] In striking contrast to this, diaza-crown ethers having -CH_2-CO-NH-CHR-CO-OR′ (-gly-gly-OR′ when R = H) sidearms exhibit much higher cation binding strengths than do the parent systems. The 12-membered and 18-membered ring derivatives having -gly-gly-OR′ sidearms show binding constants of $10^{4.32}$ and $10^{6.7}$ respectively. Divalent calcium binding by 18-crown-6 decreases from $10^{3.9}$ to $10^{0.5}$–$10^{1.8}$ when the solvent is changed from methanol to more polar water. Compound (**2**) shows the same tendency ($10^{6.7} \rightarrow 10^{4.6}$) but 4,10-diaza-12-crown-4 shows stronger calcium cation binding in water than in

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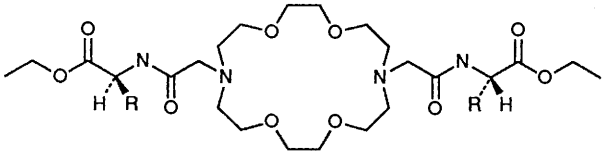
† Divalent calcium cation binding strengths were determined in H_2O at 25.0 ± 0.1 °C using an Orion Model 93-20 electrode and model 90-01 single junction reference electrode. It should be noted that with the high binding compounds, the free Ca^{2+} concentration is so low that it is below the linear response range of the electrode. For the Orion calcium electrode used in these experiments, the systems with high binding exhibited free ionic activities corresponding to concentrations of $\leq 10^{-7}$ mol dm^{-3} calcium ion. Electrode response becomes non-linear below about 10^{-4} mol dm^{-3}. We, thus, used solution concentrations as close to the unknown as possible and report K_S values in such cases only to one decimal place.

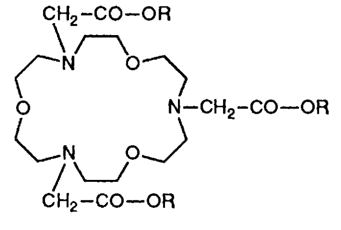
Table 1. Cation binding and selectivity values for various macrocyclic ligands.

Ligand	Solvent	log K_S		Selectivity Ca^{2+}/Na^+	Ref.
		Ca^{2+}	Na^+		
15-crown-5	MeOH	2.36	3.24	0.13	3
15-crown-5	H_2O	[a]	0.79	—	8
18-crown-6	MeOH	3.9[b]	4.35	0.35	3
18-crown-6	H_2O	0.5—1.8	0.5—1.8	*ca.* 1	8
[2.1.1]-cryptand	MeOH	6.4[c]	5.43	9.3	9
[2.1.1]-cryptand	H_2O	2.8	3.0	0.6	9—12
[2.2.1]-cryptand	MeOH	9.4[c]	9.92	3.3	9—12
[2.2.1]-cryptand	H_2O	6.9	5.4	31.6	9,10,13
[2.2.2]-cryptand	MeOH	8.0	8.14	1.3	9,10,14
[2.2.2]-cryptand	H_2O	4.5	3.9	4.0	9,13,15
DA-12-c-4(gly-gly-OMe)$_2$[d]	MeOH	3.78	2.84	8.7	
DA-12-c-4(gly-gly-OMe)$_2$	H_2O	4.32	[e]	—	
DA-15-c-5(CH_2CH_2OMe)$_2$	MeOH	4.97	5.09	0.8	
DA-15-c-5(CH_2COOEt)$_2$	MeOH	6.04	5.34	5.0	
DA-18-c-6(CH_2CH_2OMe)$_2$	MeOH	4.48	4.75	0.5	
DA-18-c-6(CH_2CH_2OH)$_2$	MeOH	6.0	4.87	13	
DA-18-c-6(CH_2COOEt)$_2$	MeOH	6.8	5.51	19	
DA-18-c-6(CH_2COOEt)$_2$	H_2O	4.26	2.0	182	
DA-18-c-6(gly-gly-OMe)$_2$	MeOH	[f]	3.37	—	
DA-18-c-6(gly-gly-OMe)$_2$	H_2O	6.7	2.2	$>10^4$	
DA-18-c-6(gly-gly-OEt)$_2$	H_2O	6.6	2.2	$>10^4$	
DA-18-c-6(gly-ala-OMe)$_2$	MeOH	[f]	4.12	—	
DA-18-c-6(gly-ala-OEt)$_2$	H_2O	7.8[g]	2.2	$>10^5$	
DA-18-c-6(gly-val-OEt)$_2$	H_2O	7.7	2.2	$>10^5$	
DA-18-c-6(gly-leu-OMe)$_2$	MeOH	[f]	4.22	—	
DA-18-c-6(gly-leu-OMe)$_2$	H_2O	7.8	2.3	$>10^5$	
TA-18-c-6(CH_2COOEt)$_3$[h]	MeOH	6.70	5.13	37	
TA-18-c-6(CH_2COOEt)$_3$	H_2O	4.62	1.9	525	

[a] Not reported. [b] Average of two or more reported values. [c] Average of three or more reported values. [d] DA means '4,10-diaza.' [e] Not determined. [f] Could not be determined, see text. [g] This value was 7.1 in 40 mM NaCl. [h] TA means '4,10,16-triaza.'



(1)



(2)

methanol when the two sidearms are -gly-gly-OMe. When we previously studied cation binding strengths of bibracchial lariat ethers having dipeptide sidearms[5] [*i.e.* dipeptide BiBLEs, **(1)**], we were unable to determine their calcium cation binding strengths in methanol because they were apparently beyond the scope of our method[3] which requires competition with another cation such as K^+ or Na^+. In water, we have now observed binding constants in the range of 10^5—10^8 for 18-membered rings having two or three sidearms (see Table 1).

Even more remarkable is the selectivity observed for these systems. We have previously shown that cation binding selectivity in the 3*n*-crown-*n* series[3] depends on several factors unrelated to 'hole size' *per se*. The cryptands[16] are more rigid molecules having well-defined interior cavities and these compounds show high size-based selectivities. For example, [2.2.1]-cryptand, a strong Ca^{2+} binder in methanol shows a Ca^{2+}/K^+ selectivity of 26 and a corresponding Na^+/K^+ selectivity of 8. This compound's Ca^{2+}/Na^+ selectivity is only 3.3. The highest hole-size selectivity is observed for [2.1.1]-cryptand which selects Ca^{2+}/K^+ by a factor of 1350. It is at the expense of binding strength generally since the K^+ affinity is only $10^{2.3}$ compared with $10^{8.5}$ for [2.2.1] and $10^{10.6}$ for [2.2.2]. Moreover, the Ca^{2+}/Na^+ selectivity of [2.1.1] is 0.11. In striking contrast to this, the dipeptide lariat ether compounds shown exhibit cation binding constants for Ca^{2+} of 10^4 to 10^8 in water, and the best selectivity we have observed, thus far, is $\geq 10^5$. Diaza-12-crown-4 having two -gly-gly-OCH_3 sidearms is a stronger binder in water than in methanol ($\log_{10} K_S = 4.32$ *vs.* 3.78, respectively). Triaza-18-crown-6 having three -gly-OEt sidearms shows a decrease in binding strength between methanol and water of about 10^2, as observed for both the cryptand and crown series (see above).

The origin of these remarkable binding strengths and selectivities almost certainly lies in the polarity of the amide carbonyl groups. Indeed, we know from other studies that a diaza-12-crown-4 ring contributes little to binding so the dipeptide sidearms must be critically important. We also know that only one carbonyl in each sidearm complexes Na^+ in derivatives of **(1)** (solid-state data[5,17]) and we suspect that all four carbonyl groups are involved here. For comparative purposes, we have determined ΔH (kcal mol^{-1}) and $T\Delta S$ (cal deg^{-1} mol^{-1}) for Ca^{2+} binding by derivatives of (**1**) having -gly-val-OMe (**1a**) and -gly-leu-OMe (**1b**) sidearms. The values are: (**1a**), $\Delta H = -35.0$, $T\Delta S = -24.5$; (**1b**), $\Delta H = -26.3$; $T\Delta S = -15.8$. The corresponding values for Ca^{2+} with 18-crown-6 are not, to our knowledge, reported.‡ Other factors may also be important, however, and are currently under investigation. The peptide lariat ether compounds promise to become interesting and useful ligands for cation binding in aqueous solution.

We warmly thank the National Institutes of Health for a grant (GM 36262) that supported this work.

Received, 14th June 1990; Com. 0/02140G

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‡ These and other thermochemical data will be included in the full report of this work.